Randomized Controlled Trial of Moxifloxacin Compared With Piperacillin–Tazobactam and Amoxicillin–Clavulanate for the Treatment of Complicated Intra-abdominal Infections

Mark A. Malangoni, MD, James Song, PhD,† Janet Herrington, PhD,† Shurjeel Choudhri, MD,† and Peter Pertel, MD, MPH†*

Objective: To compare the safety and efficacy of sequential intravenous (IV) to oral (PO) moxifloxacin treatment against a standard antimicrobial regimen of IV piperacillin–tazobactam followed by PO amoxicillin–clavulanate for the treatment of adults with complicated intra-abdominal infection (cIAI).

Summary Background Data: cIAIs are commonly due to mixed aerobic and anaerobic bacteria and require both source control and broad-spectrum antibiotic therapy.

Methods: A prospective, double-blind, randomized, phase III comparative trial. Patients with cIAI were stratified by disease severity (APACHE II score) and randomized to either IV/PO moxifloxacin (400 mg q24 hours) or comparator (IV piperacillin–tazobactam [3.0/0.375 g q6 hours] ± PO amoxicillin–clavulanate [800 mg/114 mg q12 hours]), each for 5 to 14 days. The primary efficacy variable was clinical cure rate at the test-of-cure visit (days 25–50). Bacteriologic outcomes were also determined.

Results: Of 656 intent-to-treat patients, 379 (58%) were valid to assess efficacy (183 moxifloxacin, 196 comparator). Demographic and baseline medical characteristics were similar between the 2 groups. Clinical cure rates at test-of-cure were 80% (146 of 183) for moxifloxacin versus 78% (153 of 196) for comparator (95% confidence interval, −7.4%, 9.3%). The clinical cure rate at test-of-cure for hospital-acquired cIAI was higher with moxifloxacin (82%, 22 of 27) versus comparator (55%, 17 of 31; $P = 0.05$); rates were similar for community-acquired infections (80% [124 of 156] versus 82% [136 of 165], respectively). Bacterial eradication rates were 78% (117 of 150) with moxifloxacin versus 77% (126 of 163) in the comparator group (95% confidence interval, −9.9%, 8.7%).

Conclusions: Once daily IV/PO moxifloxacin monotherapy was as least as effective as standard IV piperacillin–tazobactam/PO amoxicillin–clavulanate dosed multiple times daily for the treatment of cIAIs.

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Complicated intra-abdominal infections (cIAI) require either operative intervention or percutaneous drainage.[1] These infections are typically polymicrobial and caused by bacterial species normally present within the gastrointestinal tract.[1–3] The microbiology of cIAI varies according to the primary process site and whether the infection is community- or hospital-acquired.[1] Enterobacteriaceae are the most frequently isolated organisms, with *Escherichia coli* being the most common.[2] However, other Gram-positive and Gram-negative aerobes and anaerobes are often present in varying combinations, including *Bacteroides fragilis* and other *Bacteroides* spp., *Enterococcus* spp., *Streptococcus* spp., *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp., *Peptostreptococcus* spp., and *Clostridium* spp. Hospital-acquired infections are often caused by antibiotic-resistant organisms such as *Pseudomonas aeruginosa*, *Enterobacter* spp., *Proteus* spp., methicillin-resistant *Staphylococcus aureus*, and *Enterococcus* spp.[1]

Although the underlying cause and microbiology may vary, the general treatment approach in all cIAIs is similar, usually requiring intervention and appropriate antimicrobial therapy.[1,3] While there is no ideal agent, studies have shown that treatment is more effective when antimicrobial activity encompasses both aerobes and anaerobes, including *B. fragilis*.[4] In the absence of effective empiric therapy, failure and mortality rates are increased.[5–9] It is generally accepted that empiric antimicrobial therapy should be started as soon as cIAI is suspected. When reliable culture data are available, specific antibiotics should be used to treat the organisms isolated.[1] Recommended empiric treatment choices for cIAI include β-lactam/β-lactamase inhibitor combinations or carbapenems, or regimens that combine an antimicrobial effective against *B. fragilis* (usually metronidazole

From the *Case Western Reserve University, MetroHealth Medical Center, Cleveland, OH; and †Bayer HealthCare, Pharmaceuticals, West Haven, CT.

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Reprint request and corresponding author: Mark A. Malangoni, MD, Department of Surgery H914, Case Western Reserve University, MetroHealth Medical Center, 2500 Metro Health Drive, Cleveland, OH 44109-1998. E-mail: mmalangoni@metrohealth.org.

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or clindamycin) with a cephalosporin, fluoroquinolone, or monobactam.[1,10]

Moxifloxacin is a broad-spectrum fluoroquinolone with good activity against aerobic and anaerobic pathogens commonly isolated from patients with cIAI.[11,12] It is well absorbed from the gastrointestinal tract with a bioavailability of approximately 90%,[13] and penetrates and accumulates in human gastrointestinal mucosal tissue.[14] Dosage adjustments are unnecessary when switching from intravenous (IV) to oral (PO) forms,[15] or in patients with renal impairment (including patients requiring dialysis) or mild to moderate hepatic insufficiency.[16,17] Thus, monotherapy with moxifloxacin represents a viable treatment option for the management of patients with cIAI.

The objective of the current study was to compare the safety and efficacy of sequential IV to PO moxifloxacin against a standard antimicrobial regimen of IV piperacillin–tazobactam followed by PO amoxicillin–clavulanate for the treatment of adults with cIAI.

PATIENTS AND METHODS

Study Design and Protocol

In this prospective, randomized, double-blind, comparative, multicenter clinical trial in adult patients with cIAI, patients were stratified by disease severity using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score (stratum 1 = APACHE II score <20; stratum 2 = APACHE II score 20–35) and randomized to either sequential (IV/PO) moxifloxacin, 400 mg IV every 24 hours, followed by moxifloxacin, 400 mg PO every 24 hours (Bayer HealthCare, Pharmaceuticals, West Haven, CT), or piperacillin–tazobactam, 3.0/0.375 g IV every 6 hours, followed by amoxicillin–clavulanate, 800/114 mg PO every 12 hours (comparator agents were supplied by Bayer HealthCare, Pharmaceuticals or sourced from study site pharmacies if approved by sponsors). The duration of combined IV/PO treatment was 5 to 14 days. The decision to switch from IV to PO administration was made by the investigator, who was blinded to treatment group, and was based on the patient's clinical status and ability to tolerate oral therapy.

The study was conducted according to the Declaration of Helsinki and the regulations of the United States Food and Drug Administration. In addition, Canadian sites adhered to the Therapeutic Products Directorate regulations, and sites in Israel adhered to the regulations set forth by the Ministry of Health. Written informed consent was obtained from each patient prior to receiving the first dose of study drug, and the institutional review board at each participating site approved the protocol.

Double-blinded randomization was performed per patient using a computer-generated code provided by the sponsors; all treatments were matched in frequency and appearance, using placebo preparations where necessary, to maintain blinding. The pharmacist at each study site was responsible for initiating and maintaining the integrity of the double blind.

Patients

Hospitalized patients ≥18 years of age were eligible for enrollment if they had a known or suspected cIAI plus anticipated treatment duration of ≥5 days. Patients had to be scheduled for a laparotomy or percutaneous aspiration and meet at least 3 of the following 5 criteria: fever (>38.5°C [101.3°F] rectal; >37.0°C [98.6°F] axillary; >37.5°C [99.5°F] oral/tympanic); leukocytosis (white blood cell count ≥12,000 cells/mm^3); symptoms referable to the abdominal cavity (eg, anorexia, nausea, vomiting, pain); signs of intra-abdominal infection, eg, tenderness (±rebound), involuntary guarding, absent or diminished bowel sounds, or abdominal wall rigidity; radiologic evidence of gastrointestinal perforation or localized collections of potentially infected material. In addition, percutaneous aspiration had to show purulent material from the abdominal cavity or laparotomy had to reveal one or more of the following: gross peritoneal inflammation with purulent exudates; intra-abdominal abscess; or macroscopic contamination with gastrointestinal perforation.

Patients with cIAI included those with intra-abdominal abscess; secondary bacterial peritonitis; appendicitis with evidence of a perforation or abscess (duration of symptoms >24 hours); acute perforations of the stomach or duodenum if not operated on within 24 hours of perforation; traumatic perforation of the small bowel (excluding the duodenum) or large bowel if not operated on within 12 hours of perforation; small bowel (excluding duodenum) or large bowel perforation unrelated to trauma; and intra-abdominal infections related to previous intra-abdominal operations.

Patients with any of the following diagnoses were excluded from the study: preexisting ascites with spontaneous bacterial peritonitis; pancreatic origin of infection; perforated peptic ulcer or traumatic upper gastrointestinal tract perforation of <24 hours duration; traumatic perforation of the small or large bowel of <12 hours duration; transmural necrosis of the intestine due to acute embolic, thrombotic, or obstructive occlusions; acute cholecystitis with infection confined to the gallbladder; nonperforated appendicitis (unless there was evidence of an abscess or peritonitis); perinephric infections; gynecologic infections; indwelling peritoneal catheter; planned multiple laparotomies; conditions requiring antibiotic irrigations of the abdominal cavity or incision; and patients requiring "open abdomen" or marsupialization (defined as planned repacking or planned debridement) techniques for management.

Additionally, patients who were pregnant or nursing and patients with any of the following medical conditions were excluded from the study: immunologic compromise, including those receiving chronic immunosuppressant therapy (>15 mg/day systemic prednisone or equivalent) or HIV seropositive with a CD4 count <200 cells/μL; neutropenia (<1000 cells/μL); renal insufficiency (serum creatinine ≥ 2.5 mg/dL) or the need for hemodialysis or peritoneal dialysis; severe hepatic insufficiency (Child-Pugh class C); known QTc prolongation or receiving medications known to increase the QTc interval; uncorrected hypokalemia; known hypersensitivity to study drugs or multivitamin infusion; preexisting hypervitaminosis; history of phenylketonuria; history of fluoroquinolone-associated tendinopathy; or infection requiring treatment with an

anti-infective agent other than the study drugs. Patients who received prior antibiotic therapy were excluded unless therapy failed and they had a subsequent positive culture.

Populations for Analysis

The safety population included patients who received at least one dose of study drug and was the same as the intent-to-treat population. The efficacy-valid population had to have a diagnosis of cIAI requiring surgery or percutaneous drainage; no other systemic antibacterial agents given during the active phase except for treatment failure; receive study drugs for ≥48 hours (if clinical failure) or ≥5 days (if clinical cure); have ≥80% compliance with study drug dosing; no protocol violations influencing treatment efficacy; and successful completion of an assessment at the test-of-cure visit. The microbiologically valid population was a subset of the efficacy-valid population, comprising those patients who had bacterial growth on pretherapy culture.

Clinical and Bacteriologic Assessments

Clinical and bacteriologic examinations, and laboratory testing relating to cIAI were performed at pretreatment (within 24 hours prior to therapy start), during treatment (day 3–5 or the day of IV/PO switch if not day 3–5), at the end of therapy (day 5–14), and at the test-of-cure visit (day 25–50 after study start).

Infections were considered to be hospital-acquired if the patient had been hospitalized for more than 2 days prior to enrollment, had an infection related to previous surgery, and had been treated with antibiotics for at least 3 days prior to enrollment, or had a medical history consistent with recent hospitalization.

Clinical response at the test-of-cure visit (the primary efficacy variable) was defined as *cure* (disappearance of acute signs and symptoms related to the infection, or sufficient improvement such that additional antimicrobial therapy was not required), *failure* (insufficient resolution of the signs and symptoms of acute infection requiring additional or alternative antimicrobial therapy or additional operation or percutaneous intervention or an outcome of failure at a previous visit), or *indeterminate* (assessment not possible for any reason). For the clinical efficacy population, indeterminate outcomes at the during treatment and end of therapy visits were to be treated as failures. For the intent-to-treat population, indeterminate outcomes were treated as failures at all visits.

Bacteriologic response was based on the results of the appropriate cultures where available. If more than one intra-abdominal pathogen was isolated, each organism was assigned a bacteriologic response. At the test-of-cure visit, bacteriologic outcomes were categorized as *eradication*: absence of baseline pathogen on culture; *presumed eradication*: absence of evaluable culture in a patient with clinical cure; *persistence*: presence of baseline pathogen in a patient with clinical failure; *presumed persistence*: absence of evaluable culture in a patient with clinical failure; *superinfection*: isolation of a nonbaseline pathogen during therapy, plus signs and symptoms of infection and the need for alternative antimicrobial therapy; or *indeterminate*.

Safety and Tolerability

Patients were evaluated by physical examination and standard serial renal, hepatic, and hematologic laboratory tests. Adverse events occurring up to 7 days post-therapy and serious adverse events and deaths occurring on or before the test-of-cure visit were recorded and tabulated by type according to the Medical Dictionary for Regulatory Affairs (MedDRA) code. Adverse event intensity (mild, moderate, or severe) and relationship to the study drug (probable, possible, unlikely, or none) were categorized by the investigator prior to unblinding. Serious adverse events included those events that were fatal, life-threatening, required hospitalization, resulted in disability, or otherwise endangered the patient. Electrocardiograms were used to calculate mean changes in uncorrected QT, QTc, QRS, and RR intervals from pretherapy by treatment group.

Statistical Analysis

The primary efficacy outcome variable was clinical response at the test-of-cure visit (day 25–50) in the efficacy-valid population. Secondary efficacy analyses were conducted for the end of therapy and during therapy assessments in the efficacy-valid population, and a confirmatory analysis was performed for the intent-to-treat and microbiologically valid populations.

A 2-sided 95% confidence interval for the weighted difference in clinical success rates between treatment groups was constructed using Mantel-Haenszel weights reflecting the number of patients in each stratum. Noninferiority was defined statistically as the lower limit of the confidence interval being greater than −10%.

Statistical summaries were provided for demographic and baseline characteristics, adverse events, and laboratory data. Categorical variables were analyzed using χ^2 tests and continuous variables using a 1-way analysis of variance model.

RESULTS

Between October 23, 2000 and April 22, 2003, 681 patients from 71 investigational centers in the United States, Canada, and Israel were randomized. Details of the study population are given in Table 1. Reasons for exclusion from the efficacy-valid population were similar between the 2 groups. Across treatment groups, a similar number of patients discontinued the study prematurely (115 in the moxifloxacin group and 102 in the comparator group). Apart from protocol violations, the most common reasons for early discontinuation were adverse events and loss to follow-up. There were a similar number of patients in this category in the 2 groups.

Demographic and baseline medical characteristics for the efficacy-valid population were comparable between the 2 treatment groups (Table 2). More patients in the comparator group had APACHE II scores of ≤4 than in the moxifloxacin group (47% vs. 32%, respectively) ($P = 0.003$). There were 302 patients with abnormal pretherapy radiologic/ultrasound findings (Table 2). The 2 most common radiologic diagnoses were appendicitis (49 moxifloxacin and 55 comparator) and intra-abdominal abscess (51 moxifloxacin and 48 comparator). Only 13 patients had been hospitalized for more than 2 days before treatment. Overall, 27 patients in the moxifloxacin group

TABLE 1. Patient Population

	Moxifloxacin (no. of patients)	Comparator (no. of patients)
Patients randomized	339	342
Did not receive study drug	10	15
Safety/intention-to-treat population	329	327
Patients excluded	146	131
Use of prohibited medication	54	58
Insufficient duration of therapy	21	22
Violation of inclusion/exclusion criteria	19	12
Lost to follow-up	16	13
Insufficient surgical procedure*	9	2
Violation of the dosing schedule	8	9
Withdrawal of informed consent	8	7
Essential data missing/invalid/ inconsistent	5	4
Randomization code broken	1	2
Noncompliance with study drug	1	2
Organisms resistant to study drug	2	0
Noncompliance with protocol practice	2	0
Efficacy-valid population	183	196
Microbiologically valid population	150	165†

*Defined as a clearly inadequate operation (eg, abscess missed at operation); a surgical procedure that resulted in an unsuspected fistula in the gastrointestinal tract from unintended injury; a missed gastrointestinal tract perforation or operation that resulted in grossly ischemic intestine leading to subsequent failure.

†Two patients in the comparator group had pathogens identified from blood culture only with negative intra-abdominal culture; these were excluded from the bacteriologic efficacy analyses.

TABLE 2. Key Demographic and Infection Characteristics for Patients Valid for Clinical Efficacy

Characteristic	Moxifloxacin (183 patients)	Comparator (196 patients)
Male [n (%)]	114 (62)	131 (67)
Race [n (%)]		
White	115 (63)	110 (56)
Black	22 (12)	32 (16)
Asian	5 (3)	5 (3)
American Indian	1 (1)	1 (1)
Hispanic	40 (22)	48 (24)
Age at enrollment (yr) (mean ± SD)	47.4 ± 16.7	45.1 ± 16.5
Pretreatment APACHE II (mean ± SD)	6.9 ± 4.2	5.9 ± 4.2
Abnormal radiologic findings [n (%)]	145 (79)	157 (80)
Duration of surgery (min) (mean ± SD)	87 ± 52	86 ± 47
Blood loss during surgery (mL) (mean ± SD)	118 ± 156	136 ± 156
Hospital-acquired infections [n (%)]	27 (15)	31 (16)
Pretreatment hospitalization for >2 days [n (%)]	4 (2)	9 (5)
Infection duration prior to randomization (days) (mean ± SD)	3.7 ± 4.1	3.9 ± 4.6

and 31 patients in the comparator group had hospital-acquired infections. The most common nosocomial infections were intra-abdominal abscess (16 patients and 13 patients, respectively, in the moxifloxacin and comparator groups).

Clinical Outcomes

Clinical cure rates at the test-of-cure visit (the primary efficacy variable) in the efficacy-valid population were similar in the 2 groups (80% for moxifloxacin and 78% for comparator; 95% confidence interval, −7.4%, 9.3%, Table 3). Similarly, there were no significant differences in clinical cure rates between the 2 groups at the end-of-therapy or during-therapy visits. No patient had an outcome of "indeterminate" at the test-of-cure visit among those in the efficacy-valid population. There were no differences in clinical cure rates by infection site (Table 4).

Only 1 patient in each treatment group had an APACHE II score of ≥20; thus, the cut-off for comparison of more severe versus mild-to-moderate infection was redefined for this study as a score of ≥10. Elderly patients (>65 years) and those with more severe illness (APACHE II score ≥10) showed a good clinical response to moxifloxacin. In elderly patients, clinical cure rates were 84% (26 of 31) for moxifloxacin and 64% (16 of 25) for comparator. Clinical cure rates for patients of ≤65 years of age were 79% (120 of 152) for moxifloxacin and 80% (137 of 171) for comparator. In patients with an APACHE II of score ≥10, clinical cure rates were 76% (34 of 45) for moxifloxacin and 69% (24 of 35) for comparator. In comparison, clinical cure rates for patients with an APACHE score of <10 were 81% (112 of 138) for moxifloxacin and 80% (129 of 161) for comparator. None of these differences was statistically significant.

For patients with hospital-acquired infection, moxifloxacin provided a significantly higher cure rate (82%, 22 of 27) than the comparator (55%, 17 of 31) ($P = 0.05$). Clinical cure rates for patients with mild-to-moderate (APACHE II score <10) hospital-acquired infections were 84% (16 of 19) for moxifloxacin and 52% (12 of 23) for comparator ($P = 0.04$). Clinical cure rates for patients with more severe hospital-acquired infections (APACHE II score ≥10) were 75% (6 of 8) for moxifloxacin and 63% (5 of 8) for comparator ($P = 1.00$).

Clinical cure rates for patients with community-acquired infection were similar between the 2 treatment groups:

TABLE 3. Clinical Cure Rates in the Efficacy-Valid Population at the During-Therapy (Day 3–5), End-of-Therapy (Day 5–14), and Test-of-Cure (Day 25–50) Visits

	Clinical Cure Rate [n (%)]	
	Moxifloxacin (183 patients)	Comparator (196 patients)
During therapy visit	166 (91)	181 (92)
End of therapy visit	152 (83)	175 (89)
Test-of-cure visit*	146 (80)	153 (78)

*Primary efficacy outcome.

TABLE 4. Clinical Cure Rates by Anatomic Site at Test-of-Cure for the Efficacy-Valid Population

	Clinical Cure Rate [n/N (%)]*	
	Moxifloxacin	Comparator
Lower gastrointestinal tract infection (total)	118/150 (79)	121/153 (79)
Complicated appendicitis	84/113 (74)	91/115 (79)
Perforation of small or large bowel	25/27 (93)	19/26 (73)
Ileocolic abscess	9/10 (90)	11/12 (92)
Upper gastrointestinal tract infection (total)	13/16 (81)	15/19 (79)
Perforation of stomach or duodenum	7/8 (87)	8/10 (80)
Other†	6/8 (75)	7/9 (78)
Postoperative upper gastrointestinal tract infection	8/9 (89)	5/7 (71)
Postoperative lower gastrointestinal tract infection	7/8 (87)	12/17 (71)

*n/N = number of patients cured/total number with infection at that site.
†Complicated cholecystitis or cholangitis (3 moxifloxacin, 2 comparator), intra-abdominal abscess (3 moxifloxacin, 3 comparator); miscellaneous upper gastrointestinal tract infections (2 moxifloxacin, 4 comparator).

moxifloxacin 80% (124 of 156) versus comparator 82% (136 of 165). Clinical cure rates for patients with mild-to-moderate community-acquired infection were 81% (96 of 119) for moxifloxacin and 85% (117 of 138) for comparator. Clinical cure rates for patients with more severe community-acquired infections were 75% (28 of 37) for moxifloxacin and 70% (19 of 27) for comparator. None of these differences was statistically significant.

Bacteriologic Outcomes

The microbiologically valid population included 150 moxifloxacin-treated and 165 comparator-treated patients. However, 2 comparator-treated patients had pathogens identified from blood cultures but negative culture from intra-abdominal sites (1 patient had *E. coli* and the other *P. aeruginosa*) and were excluded from the analysis of bacteriologic efficacy (both patients had presumed eradications). Among patients with polymicrobial infections, 487 organisms were isolated from 126 moxifloxacin-treated patients and 538 from 129 comparator-treated patients. The mean number of organisms per patient was 3.9 ± 1.7 in the moxifloxacin group and 4.2 ± 1.9 in the comparator group. The 5 most frequently isolated organisms were *E. coli* (n = 177), *B. fragilis* (n = 91), *Streptococcus anginosus* (n = 82), *B. thetaiotaomicron* (n = 74), and *P. aeruginosa* (n = 45).

The bacteriologic success rate (eradication/presumed eradication) was 78% (117 of 150) in the moxifloxacin and 77% (126 of 163) in the comparator group (95% confidence interval, −9.9%, 8.7%). The success rate was 78% (128 of 165) in the comparator group if the 2 patients with bacteremia but negative intra-abdominal cultures are included. In monomicrobial infections, bacteriologic success rates were 83% (20 of 24) for moxifloxacin and 88% (30 of 34) for comparator, while for polymicrobial infections the bacteriologic success rates were 77% (97 of 126) and 74% (96 of 129), respectively. Bacteriologic success rates at the test-of-cure visit were similar in the 2 treatment groups when stratified by causative pathogen with at least 10 isolates in each treatment arm (Table 5).

The moxifloxacin minimal inhibitory concentration at which 90% of organisms are inhibited (MIC_{90}) was generally ≤1 mg/L against Gram-positive (with the exception of *Enterococcus faecalis*) and Gram-negative aerobes (with the exception of *P. aeruginosa*, data not shown). MIC_{90} values for moxifloxacin tended to be higher for anaerobic organisms. The MIC_{90} values for piperacillin–tazobactam and amoxicillin–clavulanate were generally similar to those for moxifloxacin against Gram-positive aerobes (with the exception of *E. faecalis*) but tended to be higher against Gram-negative aerobes.

Moxifloxacin had significantly higher bacteriologic efficacy in hospital-acquired infections (83% vs. 55% in the comparator group; $P = 0.04$, Table 6). Bacteriologic success rates for patients with community-acquired infections were similar between the 2 groups (77% and 82%, respectively, for moxifloxacin and comparator). Bacteriologic success rates at the test-of-cure visit were greater for hospital-acquired infections in the moxifloxacin group than in the comparator group. The exception was *S. anginosus*, for which the bacteriologic success was similar with both treatment regimens. For those organisms that were isolated from both hospital-acquired and community-acquired infections, the MIC_{90} values for moxifloxacin were the same or higher for hospital-acquired isolates than for community-acquired isolates (data not shown). The same tended to be true for the MIC_{90} values for the 2 drugs in the comparator regimen, although there were exceptions (*E. faecalis, B. thetaiotaomicron*).

TABLE 5. Bacteriologic Response at the Test-of-Cure Visit for Microbiologically Valid Patients (Organisms With ≥10 Isolates in Each Treatment Arm)

	Bacteriologic Eradication [n/N (%)]*	
Organism	Moxifloxacin (150 patients)	Comparator (163 patients)
Gram-positive aerobes		
S. anginosus	25/34 (74)	39/48 (81)
S. constellatus	18/30 (60)	10/15 (67)
E. faecalis	8/11 (73)	8/15 (53)
E. avium	13/14 (93)	9/13 (69)
Gram-negative aerobes		
E. coli	67/87 (77)	69/90 (77)
K. pneumoniae	9/15 (60)	14/24 (58)
P. aeruginosa	18/23 (78)	14/22 (64)
Gram-negative anaerobes		
B. fragilis	35/41 (85)	36/50 (72)
B. thetaiotaomicron	29/36 (81)	27/38 (71)
B. uniformis	12/14 (86)	9/12 (75)
Monomicrobial infections	20/24 (83)	30/34 (88)
Polymicrobial infections	97/126 (77)	96/129 (74)

*Includes eradication and presumed eradication; n/N = number eradicated/total number of isolates.

TABLE 6. Bacteriologic Response at Test-of-Cure Visit for Microbiologically Valid Patients

	Bacteriologic Eradication [n/N (%)]*			
	Hospital-Acquired Infection		Community-Acquired Infection	
Organism	Moxifloxacin	Comparator	Moxifloxacin	Comparator
Gram-positive aerobes				
S. anginosus	7/8 (87)	4/4 (100)	18/26 (69)	35/44 (80)
S. constellatus	—	—	17/27 (63)	8/13 (62)
E. faecalis	4/4 (100)	2/6 (33)	4/7 (57)	6/9 (67)
E. avium	—	—	13/14 (93)	6/9 (67)
Gram-negative aerobes				
E. coli	9/9 (100)	6/10 (60)	57/78 (73)	63/80 (79)
K. pneumoniae	—	—	8/14 (57)	12/17 (71)
P. aeruginosa	—	—	17/22 (77)	13/18 (72)
Gram-negative anaerobes				
B. fragilis	5/6 (83)	4/9 (44)	30/35 (86)	32/41 (78)
B. thetaiotaomicron	2/2 (100)	6/9 (67)	27/34 (79)	21/29 (72)
B. uniformis	—	—	10/12 (83)	8/11 (73)
Total	20/24 (83)	16/29 (55)	97/126 (77)	110/134 (82)

*n/N indicates number eradicated/total number of isolates; —, fewer than 10 isolates in that setting.

Failure of Bacteriologic Eradication

The most common intra-abdominal organisms isolated from patients with clinical failure were *E. coli* (46 isolates), *B. thetaiotaomicron* (25 isolates), *B. fragilis* (21 isolates), *S. anginosus* (20 isolates), *Streptococcus constellatus* (19 isolates), *K. pneumoniae* (15 isolates), and *P. aeruginosa* (15 isolates). Bacterial persistence (including presumed persistence and indeterminate outcome) of these organisms in patients with clinical failure was similar in both groups. The moxifloxacin MIC_{90} values were the same or higher for isolates from patients who failed therapy compared with those who were treated successfully (data not shown) with the exception of *K. pneumoniae*. The same tended to be true for the MIC_{90} values for the 2 comparator drugs.

Safety and Tolerability

The incidence of adverse events due to any cause was similar for the 2 groups: 84% (276 of 329) for moxifloxacin and 83% (271 of 327) for comparator. The nature of the adverse events was similar between the 2 groups, with the majority of mild or moderate intensity (88% in both treatment groups). The most common adverse events were nausea, hypokalemia, abdominal pain, and constipation (Table 7). The incidence of drug-related adverse events was 25% (82 of 329) in the moxifloxacin and 28% (90 of 327) in the comparator group and the type of adverse events was similar between the two. Premature discontinuations due to an adverse event were reported for 34 patients (10.3%) in the moxifloxacin (13 drug-related) and 28 (8.6%) in the comparator group (13 drug-related). The most common adverse events leading to premature discontinuation were treatment failure (n = 7), nausea (n = 5), and rash (n = 4). Serious adverse events occurred in 19% (63 of 329) of patients in the moxifloxacin group and 20% (66 of 327) in the comparator group. The most common serious adverse events included abdominal abscess (8 moxifloxacin vs. 15 comparator), wound infection (5 moxifloxacin vs. 6 comparator), small intestinal obstruction (6 moxifloxacin vs. 2 comparator) and pelvic abscess (5 moxifloxacin vs. 2 comparator), with no significant differences between the groups. Drug-related serious adverse events were reported for 10 patients (11 events) in the moxifloxacin group and for 7 patients (7 events) in the comparator group. Six deaths were reported in the moxifloxacin group and 7 in the comparator group. None of the deaths were thought to be related to study drug therapy by the investigators. Causes of death were related to cardiac-pulmonary failure or cardiac arrest for 6 patients, pulmonary embolism for 2 patients, or intra-abdominal abscess with respiratory failure, metastatic liver cancer, anoxic encephalopathy, massive cerebral vascular accident, or perforated colon for 1 patient each.

TABLE 7. Overview of Most Common Adverse Events Due to Any Cause (Occurrences ≥10 Patients in Either Group)

Adverse Event	Moxifloxacin (329 patients) [n (%)]	Comparator (327 patients) [n (%)]
Nausea	57 (17)	37 (11)
Constipation	44 (13)	33 (10)
Hypokalemia	40 (12)	39 (12)
Abdominal pain	36 (11)	42 (13)
Insomnia	31 (9)	36 (11)
Anemia	28 (9)	36 (11)
Diarrhea	27 (8)	39 (12)

DISCUSSION

In this study, monotherapy with sequential IV to PO moxifloxacin dosed once daily was as effective and well tolerated as a standard multidose regimen of IV piperacillin-tazobactam followed by PO amoxicillin–clavulanate in the treatment of patients with cIAI. Moxifloxacin was also effective at eradicating the most common aerobic and anaerobic bacteria causing cIAI, including *E. coli* and *B. fragilis*.

Recent guidelines for the treatment of mild-to-moderate community-acquired cIAI recommend agents such as ampicillin–sulbactam and ertapenem as well as combinations such as cefazolin and metronidazole.[1,10] Potential treatments for more severe community-acquired infections include regimens such as imipenem–cilastatin, piperacillin–tazobactam, and meropenem as well as third- or fourth-generation cephalosporins plus metronidazole.[1] Fluoroquinolones are recommended for mild-to-moderate community-acquired infections in combination with metronidazole and only ciprofloxacin in combination with metronidazole is recommended for severe infections.[1] In this trial, monotherapy with moxifloxacin was as effective as a standard comparator regimen in the treatment of both mild-to-moderate (APACHE II score <10) and more severe (APACHE II score ≥ 10) community-acquired cIAI.

Because hospital-acquired intra-abdominal infections are often caused by more resistant bacteria, treatment may require combination regimens selected on the basis of local susceptibility patterns.[1] In this study, the organisms causing the hospital-acquired infections tended to have higher MIC_{90} values for moxifloxacin (as well as for the 2 drugs in the comparator regimen) than the community-acquired organisms. Despite this, for hospital-acquired infections, moxifloxacin provided a higher clinical cure rate (82% vs. 55%; $P = 0.05$) and bacteriologic cure rate (83% vs. 55%; $P = 0.04$) than the comparator regimen. In addition, moxifloxacin was effective for both mild-to-moderate and more severe hospital-acquired infections providing clinical cure rates of 84% and 75%, respectively.

Analysis of disease severity by APACHE II score did not indicate any significant differences in efficacy for moxifloxacin with APACHE II scores 0 to 9 or ≥ 10 (success rates of 81% and 76%, respectively; $P = 0.79$). These results should be interpreted with caution, however, as they are based on a relatively small sample size and need to be confirmed in a larger patient group. Also, as there were only 2 patients with an APACHE II score of ≥ 20, fluoroquinolone monotherapy needs to be further evaluated in more critically ill patients.

A previous report has demonstrated more favorable outcomes for patients with cIAI who are enrolled in prospective randomized clinical trials.[18] Patients not entered in these studies tend to be older and have higher APACHE II scores than patients in clinical trials. Newer agents also have a lower incidence of antimicrobial resistance, which is associated with a decreased incidence of treatment failure. This may account in part for the better clinical cure rate with moxifloxacin treatment in the present study.

One recent surveillance study demonstrated a higher prevalence of fluoroquinolone-resistant *Bacteroides* spp. than previously reported.[11] However, this report included only isolates from 12 large tertiary care medical centers, and such studies may not reflect susceptibility rates among community-acquired pathogens. Clinical cure rates for patients infected with *B. fragilis* or *B. thetaiotaomicron* were at least as good for moxifloxacin as for the comparator regimen. Also, although the moxifloxacin MIC_{90} values (but not the values for the 2 comparator drugs) were higher for *B. fragilis* and *B. thetaiotaomicron* among patients who failed therapy, there was no correlation between individual MIC values and clinical or bacteriologic success or failure. However, this may reflect the relatively small number of patients infected with one of these organisms who subsequently failed moxifloxacin therapy.

Although comparisons between studies must be made with caution, moxifloxacin efficacy rates in the current study are consistent with those obtained with other recommended treatment regimens, including ciprofloxacin plus metronidazole, piperacillin–tazobactam, and imipenem–cilastatin.[19,20] Further studies that directly compare fluoroquinolones with or without metronidazole in cIAI need to be conducted. In addition, local susceptibility patterns to *Bacteroides* spp. should also be considered when choosing monotherapy or combination therapy.

The current trial also demonstrated that the safety and tolerability profile of moxifloxacin was similar to that of piperacillin–tazobactam and amoxicillin–clavulanate. Rates of drug-related, serious adverse events and deaths were similar for both treatment groups.

CONCLUSION

Moxifloxacin monotherapy was as well tolerated and effective as multidose therapy with IV piperacillin tazobactam followed by oral amoxicillin clavulanate in the treatment of patients with cIAI. Moxifloxacin, which can be given once daily, can be considered a useful and convenient option for the treatment of cIAI.

APPENDIX: PARTICIPATING INVESTIGATORS AND INSTITUTIONS

Canada: Dhar, Windsor Regional Hospital, Windsor, ON; N. Christou, Royal Victoria Hospital, Montreal, QC; T. Louie, Foothills Medical Center and Peter Lougheed Centre, Calgary, AB; D. Grimard, Complexe Hospitalier de la Sagamie, Chicoutimi, QC; Hayashi, Victoria General Hospital, Victoria, BC; B. Lawlor, St. Paul's Hospital, Saskatoon, SK. **Israel:** D. Zeltser, Tel Aviv Sourasky Medical Center, Tel Aviv; R. Raz, Haemek Medical Center, Afula. **United States:** S. Dulchavsky, Detroit Receiving Hospital, Detroit, MI; S. Klein, Harbor-UCLA Medical Center, Torrance, CA; J. Mazuski and M. Shapiro, St. Louis University Medical Center, St. Louis, MO; N. McSwain, Medical Center of Louisiana at New Orleans, New Orleans, LA; T. Buchman, Barnes-Jewish Hospital, St. Louis, MO; S. Cohn, University of Miami Medical Center, Miami, FL; M. Malangoni, Metro Health Medical Center, Cleveland, OH; M. Metzler, University of Missouri School of Medicine, Columbia, MO; S. Vogel, Shands Medical Plaza, Gainesville, FL; A. Yellin, Los Angeles County/University of Southern California Med Ctr, Los

Angeles, CA; R. Martindale, Medical College of Georgia Hospital and Clinics, Augusta, GA; J. Levine, Hackensack University Medical Center, Hackensack, NJ; P. Harrison, Wesley Medical Center, Wichita, KS; R. Bennion, UCLA Medical Center-Olive View, Sylmar, CA; G. Coppa, Staten Island University Hospital, Staten Island, NY; T. Fabian, Regional Medical Center at Memphis, Memphis, TN; C. O'Hare, University of Oklahoma Hospital, Oklahoma City, OK; R. Smith, Via Christi Regional Medical Center; Wichita, KS; S. Mintz, Salt Lake Regional Medical Center, Salt Lake City, UT; R. Cooney, Milton S. Hershey Medical Center, Hershey, PA; S. O'Marro, Springfield Clinic, Springfield, IL; E. Block, Orlando Regional Medical Center, Orlando, FL; J. Vazquez, Wayne State University, Detroit, MI; I. Baird, Grant/Riverside Methodist Hospital, Columbus, OH; G. Gomez, Indiana University Hospital, Indianapolis, IN; F. Remzi, The Cleveland Clinic Foundation, Cleveland, OH; P. O'Neill, Kings County Hospital Center, Brooklyn, NY; E. Carrillo and L. Lottenberg, Memorial Regional Hospital, Hollywood, FL; S. Schechter, Miriam Hospital, Providence, RI; J. Robbins, William Beaumont Hospital, Royal Oak, MI; K. Mullane, Loyola University Medical Center, Maywood, IL; N. Metzger and R. Sinha, Southern Arizona Veterans Affairs, Tucson, AZ; G. Fulda, Christiana Care Health Services, Newark, DE; A. Rally, R. Swanson and S. Heard, University of Massachusetts Medical Center, Worcester, MA; S. Tisherman, University of Pittsburgh Medical Center Health System, Pittsburgh, PA; D. Miller, Veterans Affairs Medical Center-Portland, Portland, OR; J. Clark, Exempla St. Joseph Hospital, Denver, CO; W. Hanson, University of Pennsylvania, Philadelphia, PA; C. Daggett, DO Collins Associates, Inc, Prairie Village, KS; K. Azarow and R. Place, Madigan Army Medical Center, Tacoma, WA; R. McIntyre, Jr, University of Colorado Health Sciences Center, Denver, CO; S. Fine, Jordan Valley Hospital, West Jordan, UT; J. Hunt, Medical Center of Louisiana at New Orleans, New Orleans, LA; A. Barbul, Sinai Hospital of Baltimore, Baltimore, MD; C. Mains and M. Feldman, St. Anthony Central Hospital, Denver, CO; A. Gest and C. Albarracin, Christus Spohn Hospital Memorial, Corpus Christi, TX; B. Thaemert, Avera McKennan Hospital, Sioux Falls, SD; G. Peoples and M. Woll, Walter Reed Army Medical Center, Washington, DC; G. Grindlinger, Maine Medical Center, Portland, ME; S. Nasraway, New England Medical Center, Boston, MA; J. Myers and R. Stewart, University Health System University Hospital, San Antonio, TX; L. Napolitano, VA Maryland Health Care System, Baltimore, MD; Carlos Sanchez-Sergenton, Puerto Rico Medical Center, San Juan, PR; S. Marcus, Bellevue Hospital Center, New York, NY; M. Holzman, Vanderbilt University Medical School, Nashville, TN; R. Holman, Arlington Hospital, Arlington, VA; A. Gest and C. Schrock, Infectious Diseases-Minneapolis LTD, Minneapolis, MN; R. Fetchick, San Antonio Infectious Diseases Consultants, San Antonio, TX; M. Alpert, Central Montgomery Surgical Associates, Lansdale, PA; C. Lucasti, Shore Memorial Hospital, Somers Point, NJ and Burdette Tomlin Memorial Hospital Cape May Court House, NJ; R. Quickel, Hennepin County Medical Center, Minneapolis, MN.

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